# Personalized medicine: Individualized Treatment Rules

# Definition of Precision Medicine

- Precision medicine is a medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient. In this model, diagnostic testing is often employed for selecting appropriate and optimal therapies based on the context of a patient's genetic content or other molecular or cellular analysis. Tools employed in precision medicine can include molecular diagnostics, imaging, and analytics/software.

- Making optimal healthcare decision for each individual patient based on this subject's context information.

# Illustration Data

Table: An illustration dataset

| ID | $Y$ | $A$ | $X_1$ | $X_2$ | $X_3$ | $\cdots$ |
|---|---|---|---|---|---|---|
| 1 | 1.5 | 1 | F | 26 | 7.8 | $\cdots$ |
| 2 | 1.2 | 2 | M | 28 | 8.2 | $\cdots$ |
| 3 | 2.3 | 3 | M | 31 | 8.9 | $\cdots$ |
| 4 | 0.9 | 2 | F | 35 | 9.4 | $\cdots$ |
| 5 | 1.7 | 1 | M | 22 | 7.3 | $\cdots$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\ddots$ |

## Research Question

Based on these data, how can we treat a new patient?

In other words, how can we learn a treatment assignment rule that, if followed by the entire population of certain patients, would lead to the best outcome on average?

# Three Key Components for Precision Medicine

Context based decision learning has data in 3 components:

- $X_1, X_2, \cdots, X_p$ is context information.
- $A$ is a context action.
- $Y$ is a reward.

Notes:

- This data structure differs from data for typical supervised and unsupervised learning.
- Examples on data collection for precision medicine ...

# Other Examples: Car Purchase

Table: My Friends' Rating of Their First Cars

| ID | Satisfaction | Car Type | Gender | Age | Mileage per Day | $\cdots$ |
|---|---|---|---|---|---|---|
| 1 | 90% | Focus | F | 26 | 7.8 | $\cdots$ |
| 2 | 85% | Corolla | M | 28 | 8.2 | $\cdots$ |
| 3 | 70% | Civic | M | 31 | 8.9 | $\cdots$ |
| 4 | 75% | Corolla | F | 35 | 9.4 | $\cdots$ |
| 5 | 60% | Civic | M | 22 | 7.3 | $\cdots$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\ddots$ |

Learning from these data, what car should I purchase?

# Other Examples: Business Investment

Table: Previous Commercial Investments and Returns

| Case ID | Return | Type | Month | Location | Share of Market | $\cdots$ |
|---|---|---|---|---|---|---|
| 1 | 1.2 | TV | Jan | MW | 12.5 | $\cdots$ |
| 2 | 0.9 | Radio | Oct | NE | 18.2 | $\cdots$ |
| 3 | 1.4 | Web | Nov | WE | 12.9 | $\cdots$ |
| 4 | 1.3 | Web | Dec | MW | 10.4 | $\cdots$ |
| 5 | 1.2 | Radio | Feb | SE | 11.3 | $\cdots$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\ddots$ |

Learning from these data, what is our best way to invest in New England area if our product has 12% market share in this March?

# Making Optimal Decision Based on Data

Broad applications, some examples:

- Treatment selection: which treatment is the best for this patient?
- Treatment transition: should we keep using the current treatment or consider an intensification?
- Business analytic: how to invest (among a few choices) to maximize the return?
- Recommendation system: which item should a system recommend to a customer to maximize profit?

All these problems are similar in terms of data format and analytic solutions. **Essentially, we focus on a problem of making the optimal decision based on data.**

So, what is a general framework to solve this?

# Reinforcement Learning Framework

- This problem is a special case in reinforcement learning framework which is different from supervised learning (e.g. classification) and unsupervised learning (e.g. clustering).
- Traditional alternatives (e.g. linear regression for rewards) may not be efficient to solve these problems.
- It is connected with supervised learning methods (e.g. support vector machines).
- It can be extended to multiple stage decision making to optimize treatment sequences (e.g. dynamic treatment regimes).

# Outlines

# Notations

- There are $N$ subjects from a large population.
- $A_i$ is the treatment assignment (actions), where $i = 1, \cdots, N$.
- $Y_i$ is the response assuming that larger $Y_i$ is better (rewards).
- $X_i$ is a vector of covariates.
- $(Y, A, X)$ is the generic random variable of $\{(Y_i, A_i, X_i)\}$.
- $\mathcal{P}$ is the distribution of $(Y, A, X)$.
- $E$ is the expectation with respect to $\mathcal{P}$.
- Population space $\mathcal{X}$, i.e. $X_i \in \mathcal{X}$.
- $\mathcal{D}(\cdot)$ is a treatment recommendation based on covariates, i.e. $\mathcal{D}(\cdot) : \mathcal{X} \to \mathcal{A}$.
- $\mathcal{P}^{\mathcal{D}}$ is the distribution of $(Y, A, X)$ given that $A = \mathcal{D}(X)$.

# Value Function

Define

$$E^{\mathcal{D}}(Y) = \int Y d\mathcal{P}^{\mathcal{D}} = \int Y \frac{d\mathcal{P}^{\mathcal{D}}}{d\mathcal{P}} d\mathcal{P} = E\left[\frac{I\left\{A = \mathcal{D}(X)\right\}}{p(A|X)} Y\right],$$

where we use the fact that

$$\frac{d\mathcal{P}^{\mathcal{D}}}{d\mathcal{P}} = \frac{p(y|x,a) I\{a = \mathcal{D}(x)\} p(x)}{p(y|x,a) p(a|x) p(x)} = \frac{I\{a = \mathcal{D}(x)\}}{p(a|x)}.$$

Our objective is to find $\mathcal{D}(\cdot)$ to maximize the following value function:

$$\mathcal{D}_o \in \underset{\mathcal{D} \in R}{\operatorname{argmax}} E^{\mathcal{D}}(Y) = E\left[\frac{I\left\{A = \mathcal{D}(X)\right\}}{p(A|X)} Y\right], \tag{1}$$

where $R$ is a space of possible treatment recommendations.

# Advantages of This Framework

- $Y$ is able to handle binary, continuous, time to event data type.
- $A$ is able to handle multiple treatments.
- $X$ is able to incorporate variety of variables. For example, if $X$ includes study ID, the framework can be used for meta analysis.
- $P(A|X)$ allows treatment assignments depending on covariates. So it can handle both randomized control trials and observational studies.
- It has an objective function to evaluate different treatment assignments.

# An Example to Build Intuition

Table: Example Data

| ID | $Y$ | $A$ | $X$ | $P(A\|X)$ |
|---|---|---|---|---|
| 1 | 1 | 1 | 1 | 0.5 |
| 2 | 2 | 1 | 2 | 0.5 |
| 3 | 3 | 1 | 3 | 0.5 |
| 4 | 4 | 1 | 4 | 0.5 |
| 5 | 5 | 1 | 5 | 0.5 |
| 6 | 3 | 2 | 1 | 0.5 |
| 7 | 3 | 2 | 2 | 0.5 |
| 8 | 3 | 2 | 3 | 0.5 |
| 9 | 3 | 2 | 4 | 0.5 |
| 10 | 3 | 2 | 5 | 0.5 |

Questions to think about: why is $P(A|X) = 0.5$? what do the responses look like?

# Which Doctor is Better

Suppose we have two doctors and each of them has a treatment rule. Which doctor is a better one?

- Doctor Adam: give patients treatment 1 if $X \geq 2$, and treatment 2 otherwise, denoted as $\mathcal{D}_A(X)$.
- Doctor Barry: give patients treatment 1 if $X \geq 3$, and treatment 2 otherwise, denoted as $\mathcal{D}_B(X)$.

# Example Continued

Table: Calculation Based on Table 4

| ID | $Y$ | $A$ | $X$ | $P(A\|X)$ | $\mathcal{D}_A$ | $\mathcal{D}_B$ | $\mathcal{D}_A = A$ | $\mathcal{D}_B = A$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 1 | 0.5 | 2 | 2 | 0 | 0 |
| 2 | 2 | 1 | 2 | 0.5 | 1 | 2 | 1 | 0 |
| 3 | 3 | 1 | 3 | 0.5 | 1 | 1 | 1 | 1 |
| 4 | 4 | 1 | 4 | 0.5 | 1 | 1 | 1 | 1 |
| 5 | 5 | 1 | 5 | 0.5 | 1 | 1 | 1 | 1 |
| 6 | 3 | 2 | 1 | 0.5 | 2 | 2 | 1 | 1 |
| 7 | 3 | 2 | 2 | 0.5 | 1 | 2 | 0 | 1 |
| 8 | 3 | 2 | 3 | 0.5 | 1 | 1 | 0 | 0 |
| 9 | 3 | 2 | 4 | 0.5 | 1 | 1 | 0 | 0 |
| 10 | 3 | 2 | 5 | 0.5 | 1 | 1 | 0 | 0 |

# Example Continued

Doctor Adam:

$$E^{\mathcal{D}_A(Y)} = \frac{1}{10}\left(\frac{0}{0.5}\times 1+\frac{1}{0.5}\times 2+\frac{1}{0.5}\times 3+\frac{1}{0.5}\times 4+\frac{1}{0.5}\times 5+\frac{1}{0.5}\times 3+\frac{0}{0.5}\times 3+\frac{0}{0.5}\times 3+\frac{0}{0.5}\times 3+\frac{0}{0.5}\times 3\right)$$

$$= 3.4$$

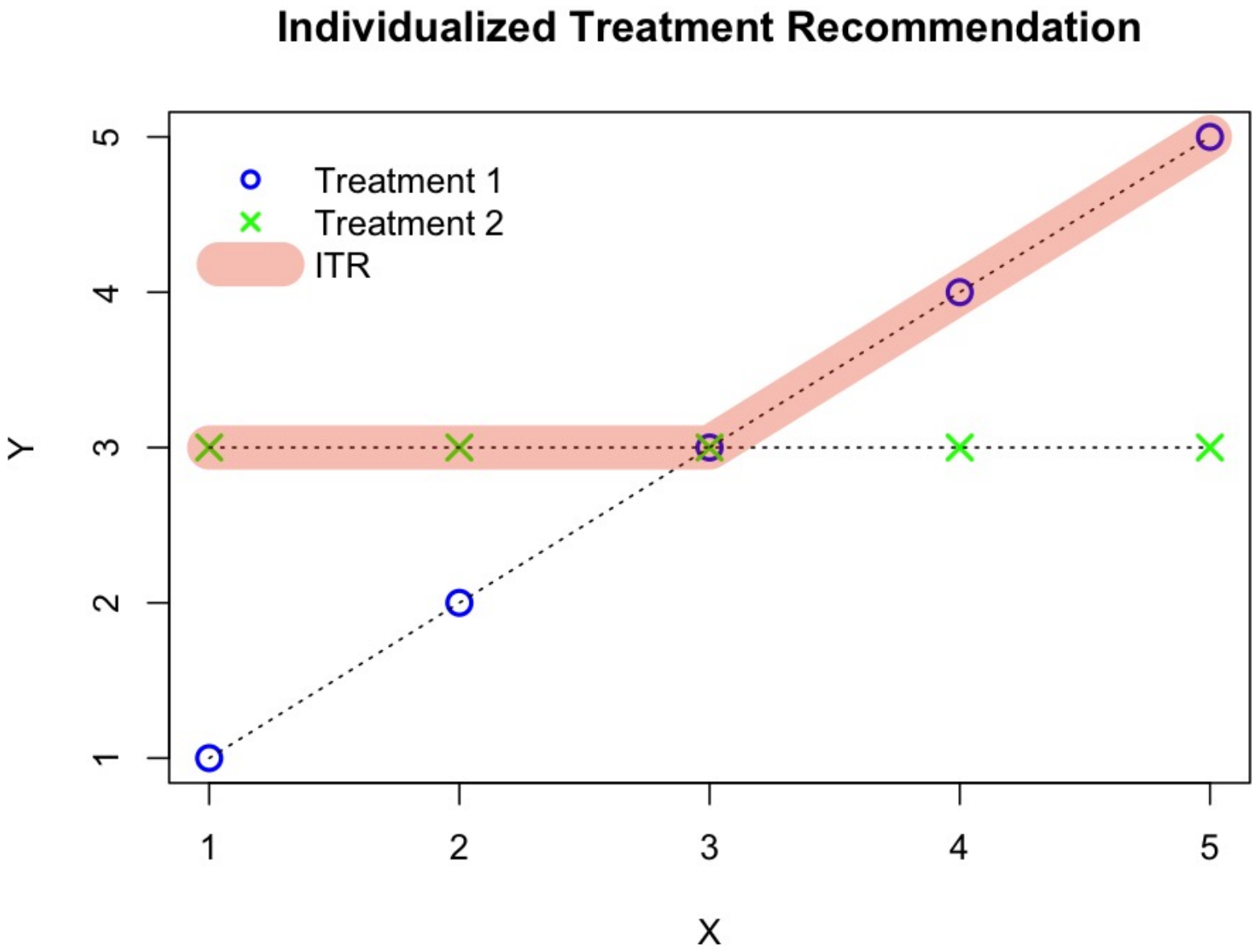
Doctor Barry:

$$E^{\mathcal{D}_B(Y)} = \frac{1}{10}\left(\frac{0}{0.5}\times 1+\frac{0}{0.5}\times 2+\frac{1}{0.5}\times 3+\frac{1}{0.5}\times 4+\frac{1}{0.5}\times 5+\frac{1}{0.5}\times 3+\frac{1}{0.5}\times 3+\frac{0}{0.5}\times 3+\frac{0}{0.5}\times 3+\frac{0}{0.5}\times 3\right)$$

$$= 3.6$$

Conclusion: Doctor Barry's rule is better than Doctor Adam's. Can we improve Doctor Barry's rule? How can we find the best rule?

# Graphic Illustration



# Thought Provoking Questions

- Both treatment 1 and treatment 2 have an average treatment effect as 3.0. But ITR generates average benefit value 3.6. Can algorithm beat a new molecule entity?
- Treatment 1 should not be only better than treatment 2. It has to be better with a non-trivial benefit margin. How can we handle this case?
- What if the treatment randomization ratio is not 1:1?
- What if we have multiple covariates? The rule can be complicated.
- What if we have multiple treatments?

# Analysis results: how ITR creates more value.

This data analysis shows how ITR creates additional value for patients. We have 1978 patients from two treatment arms, and 2 important biomarkers are selected from 35 biomarkers.

Table: *HbA1c Reduction Before and After Following ITR.* Patients with baseline fasting insulin $\geq 61.12$pmol/L and baseline HbA1c $\geq 8.1\%$ ($A_o^1$) are recommended to take Pioglitazone, otherwise ($A_o^0$ ) patients are recommended to take Gliclazide. After following ITR, the overall HbA1c reduction changes from -1.287% to -1.473%. Notes: ITR is our proposed method which is referred to as Individualized Treatment Recommendation.

| Original | | | Follow ITR | | |
|---|---|---|---|---|---|
| -1.287 | | | -1.473 | | |
| | Gliclazide | Pioglitazone | | Gliclazide | Pioglitazone |
| Mean | -1.271 | -1.303 | $A_o^1$ | -1.394 | -1.864 |
| | | | $A_o^0$ | -1.19 | -0.932 |

# Key Insights on Solving ITR

Three connections:

1. Maximization and minimization of the value function.
2. Classification and loss functions.
3. ITR and weighted classifications.

# From Maximization to Minimization

Original objective function (Qian and Murphy, 2011)

$$\mathcal{D}_o \in \underset{\mathcal{D}\in R}{\operatorname{argmax}} E^{\mathcal{D}}(Y) = E\left[\frac{I\{A=\mathcal{D}(X)\}}{p(A|X)}Y\right]. \quad (2)$$

Making connections:

$$E\left\{\frac{Y}{p(A|X)}\right\} - E\left[\frac{I\{A=\mathcal{D}(X)\}}{p(A|X)}Y\right] = E\left[\frac{I\{A\neq\mathcal{D}(X)\}}{p(A|X)}Y\right]$$

New objective function:

$$\mathcal{D}_o \in \underset{\mathcal{D}\in R}{\operatorname{argmin}} E^{\mathcal{D}}(Y) = E\left[\frac{I\{A\neq\mathcal{D}(X)\}}{p(A|X)}Y\right]. \quad (3)$$

# Empirical Evaluation

Objective function:

$$\mathcal{D}_o \quad \in \quad \underset{\mathcal{D} \in R}{\operatorname{argmin}} \, E^{\mathcal{D}}(Y) = E\left[\frac{I\left\{A \neq \mathcal{D}(X)\right\}}{p(A|X)} Y\right].$$

When we have data, we can evaluate the objective function as,
Empirical evaluation:

$$D_o \quad = \quad \underset{D \in R}{\operatorname{argmin}} \, n^{-1} \sum_{i=1}^{n} \frac{Y_i}{p(A_i|X_i)} I\left\{A_i \neq \mathcal{D}(X_i)\right\}. \tag{4}$$

# Classification Problems

A classification problem is to train a rule $\mathcal{D}(X)$ on a dataset to predict new subject membership. A simple dataset can be as below,

Table: An illustration dataset

| ID | $A$ | $X_1$ | $X_2$ | $X_3$ | $\cdots$ |
|---|---|---|---|---|---|
| 1 | 1 | F | 26 | 7.8 | $\cdots$ |
| 2 | 2 | M | 28 | 8.2 | $\cdots$ |
| 3 | 1 | M | 31 | 8.9 | $\cdots$ |
| 4 | 3 | F | 35 | 9.4 | $\cdots$ |
| 5 | 1 | M | 22 | 7.3 | $\cdots$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\ddots$ |

# Classification and Loss Function

Roughly speaking, A good classifier has smaller errors (we will add regularization later).

Classification objective function

$$D_o = \underset{D \in R}{\operatorname{argmin}}\, n^{-1} \sum_{i=1}^{n} I\left\{A_i \neq \mathcal{D}(X_i)\right\}.$$

Compare our ITR objective function below

ITR objective function

$$D_o = \underset{D \in R}{\operatorname{argmin}}\, n^{-1} \sum_{i=1}^{n} \frac{Y_i}{p(A_i|X_i)} I\left\{A_i \neq \mathcal{D}(X_i)\right\}.$$

# Important Implications and Next Steps

- We can solve the original reinforcement learning problem (ITR) as a weighted supervised learning problems (Zhao et al., 2012).
- There are vast amount of methods and literatures on solving classification problems, in particular for binary classifications.
- With some modifications, we can leverage these existing algorithms to develop our ITR algorithms.
- We will focus on the Support Vector Machine (SVM). However, many other classifiers can be tailored for this.

# Outlines

# Classification

- Observe a collection of i.i.d. training data $(X_1, a_1), (X_2, a_2), \ldots, (X_n, a_n)$ from $\mathcal{P}$.
- Covariates (inputs, features, prediction variables): $X_i = (X_{i1}, \ldots, X_{ip})$
- Response variable (class label, output):

$$a_i \in \{c_1, c_2, \ldots, c_K\}.$$

- We want to build a model $\mathcal{D}(X)$ (using the training data), so that when seeing a new input vector $X$, we can predict the output $\hat{a}$.

# Classification Errors and Loss Function

- Loss function (0/1):

$$L\{A, \mathcal{D}(X)\} = \begin{cases} 0 & \text{if } A = \mathcal{D}(X) \\ 1 & \text{if } A \neq \mathcal{D}(X) \end{cases}$$

- Misclassification error

$$\begin{aligned} R(\mathcal{D}) &= E_{\mathcal{P}} L\{A, \mathcal{D}(X)\} \\ &= P_{\mathcal{P}}[I\{A \neq \mathcal{D}(X)\}]. \end{aligned}$$

- For binary class case, Bayes optimal classifier ($A \in \{-1, 1\}$):

$$\begin{aligned} \mathcal{D}^*(X_i) &= \underset{\mathcal{D}}{\operatorname{argmin}}\, R(\mathcal{D}) \\ &= \operatorname{sgn}\left\{\Pr(A = 1 | X = X_i) - \Pr(A = -1 | X = X_i)\right\}. \end{aligned}$$

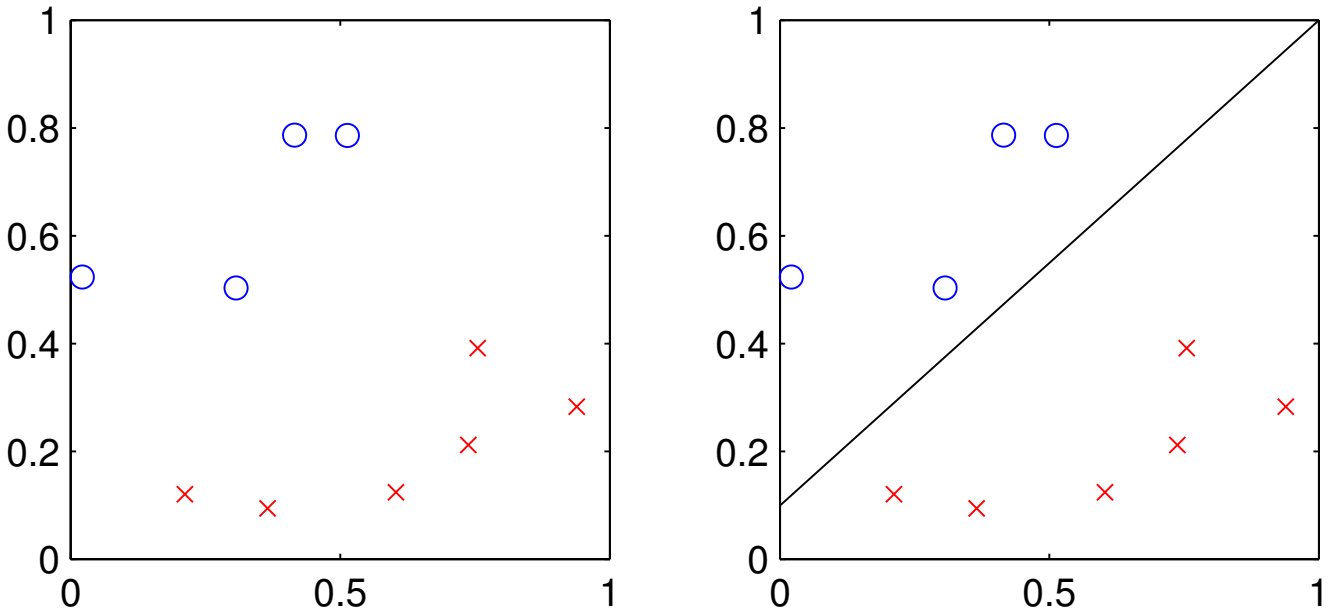
- Bayes error: $R(\mathcal{D}^*)$.

# Binary Large-Margin Classifier

- $a \in \{\pm 1\}$;
  Estimate $f(X)$ with classification rule $\text{sgn}\{f(X)\} : \mathbb{R}^d \to \{\pm 1\}$,
  $\hat{a} = +1$ if $f(X) \geq 0$ and $\hat{y} = -1$ if $f(X) < 0$.
- $A_i f(X_i)$: functional margin.
- Correction classification if $A_i f(X_i) > 0$.
- The 0–1 loss: $I\{A_i f(X_i) \leq 0\}$.

# Support Vector Machine (SVM)

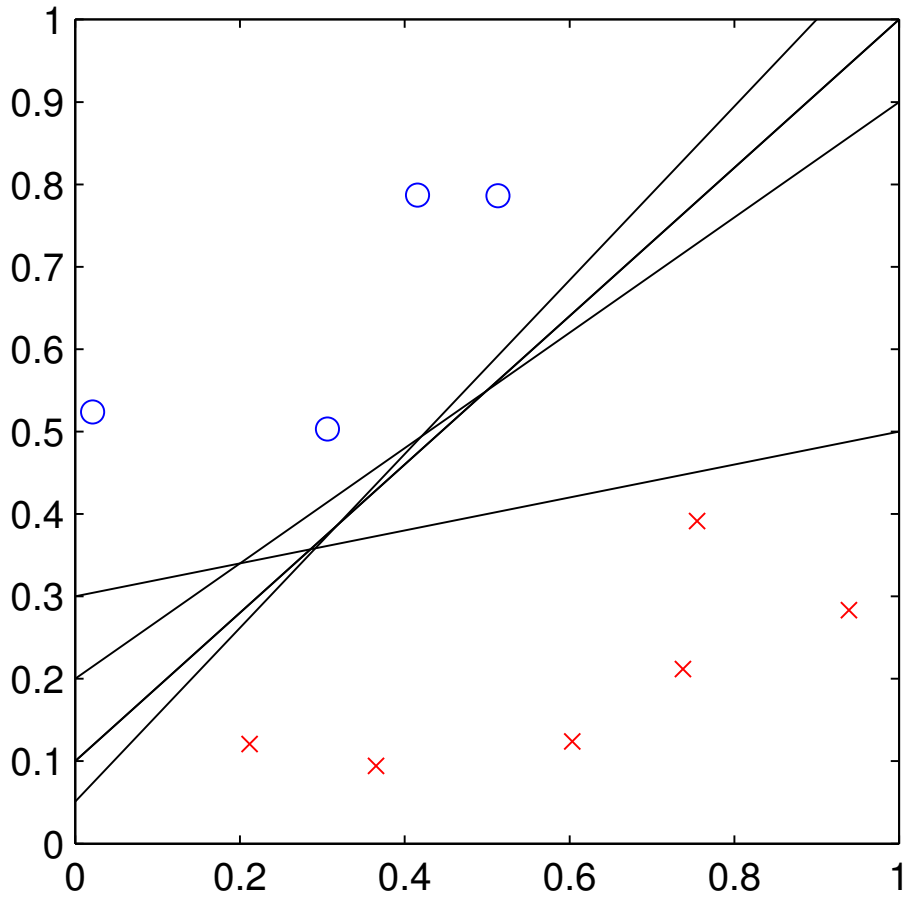
Linearly separable: Find $f(X) = \beta_0 + X^\top \beta$ to separate two groups of points.



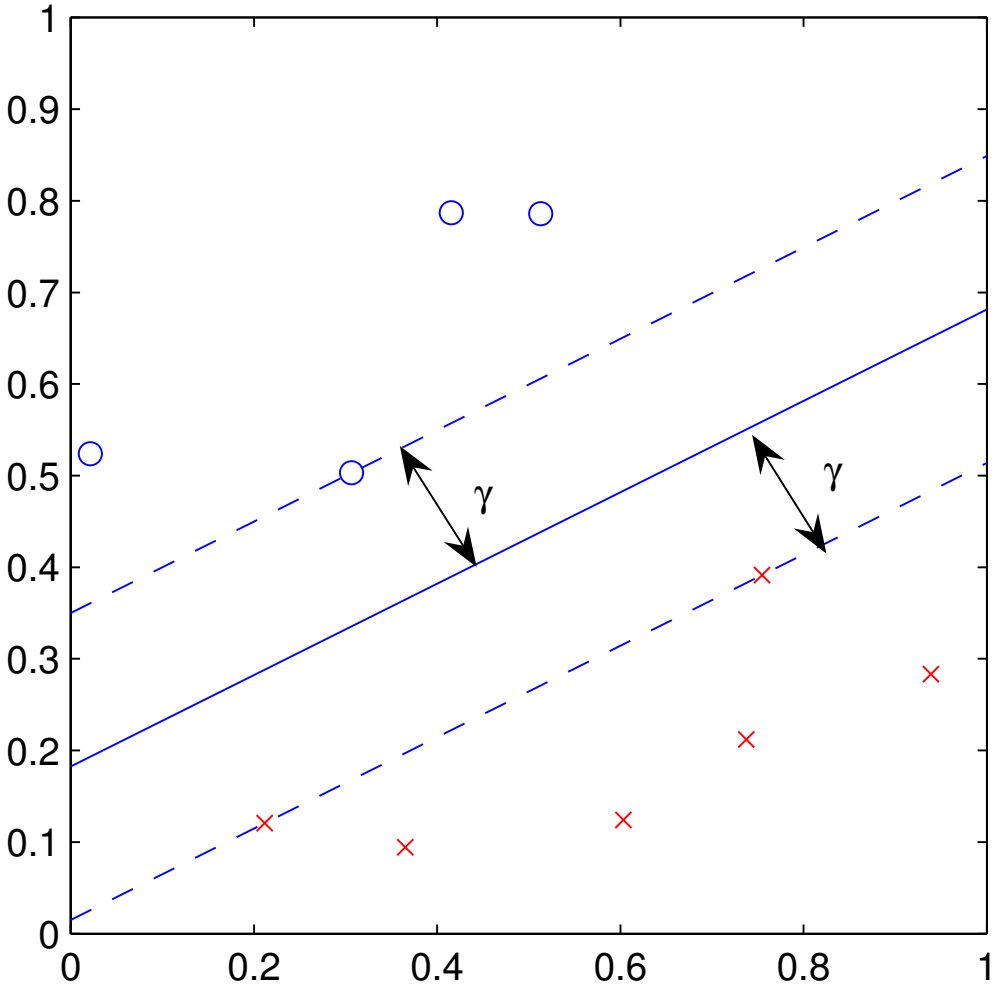

Note:

- red cross $\longleftrightarrow +1$; blue circle $\longleftrightarrow -1$.

# Which one is the best?



# SVM: Maximum Separation



# Maximum Margin Classifier

Goal: Separate two classes and maximizes the distance to the closest points from either class (Vapnik 1996)

- Unique solutions
- Better classification performance on the training data

$$\begin{aligned} \underset{\beta,\beta_0}{maximize} \quad & \gamma \\ \text{subject to} \quad & A_i(\beta_0 + X_i^\top \beta) \geq \gamma, \\ & \|\beta\| = 1. \end{aligned}$$

All the points are at least a signed distance $\gamma$ from the decision boundary

- Maximize the minimum distance
- Need constraint $\|\beta\| = 1$

# Equivalent Problem

Try to get rid of the constraint $\|\beta\|= 1$

$$\frac{1}{\|\beta\|} A_i(X_i^\top \beta + \beta_0) \geq \gamma,$$

or equivalently

$$A_i(X_i^\top \beta + \beta_0) \geq \gamma \|\beta\|$$

Any positively scaled $(\beta, \beta_0)$ also satisfies this inequality. We set $\|\beta\|= \frac{1}{\gamma}$. Then the objective function $\gamma = 1/\|\beta\|$, and

$$\begin{aligned} \underset{\beta,\beta_0}{minimize} \quad & \frac{1}{2}\|\beta\| \\ \text{subject to} \quad & A_i(X_i^\top \beta + \beta_0) \geq 1, \quad \forall i = 1, ..., n. \end{aligned}$$

Linear SVM for perfectly separable cases.
Note: by definition $1/\|\beta\|$ is the width of margin.

# Optimal Hyperplane of SVM

$$\begin{aligned} \text{minimize} \quad & \frac{1}{2}\|\beta\|^2 \\ \text{subject to} \quad & A_i(\langle \beta, X_i \rangle + \beta_0) - 1 \geq 0, \quad \forall i = 1, 2, \cdots, n. \end{aligned}$$

- Lagrange function is :

$$L_P(\beta, \beta_0, \alpha) = \frac{1}{2}\|\beta\|^2 - \sum_{i=1}^{n} \alpha_i \{A_i(\langle \beta, X_i \rangle + \beta_0) - 1\}$$

- For any fixed $\alpha$:

$$\begin{cases} \frac{\partial L(\beta, \beta_0, \alpha)}{\partial \beta_j} = 0, & j = 1, 2, \cdots, p \\ \frac{\partial L(\beta, \beta_0, \alpha)}{\partial \beta_0} = 0 \end{cases} \Longrightarrow \begin{cases} \beta = \sum_{i=1}^{n} \alpha_i A_i X_i \\ 0 = \sum_{i=1}^{n} \alpha_i A_i \end{cases}$$

# The Dual Problem

$$\begin{aligned} \text{maximize} \quad & L_D(\alpha) = \sum_{i=1}^{n} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{n} \alpha_i \alpha_j A_i A_j \langle X_i, X_j \rangle \\ \text{subject to} \quad & \alpha_i \geq 0, \quad i = 1, 2, \cdots, n \\ & \sum_{i=1}^{n} \alpha_i A_i = 0. \end{aligned}$$

This optimization is a quadratic programming problem and can be solved using classical optimization software. We are going to provide details on implementation in the R hands on example.

# Primal vs. Dual

- Minimize $L_P$ with respect to primal variables $\beta_0, \beta$
- Maximize $L_D$ with respect to dual variables $\alpha_i$
- Maximizing the dual is often a simpler convex QP than the primal, in particular when $p \gg n$.

# Recovering the Optimal Hyperplane

- The optimizer of the dual: $\alpha^*$
- $\beta^*$ is given by:

$$\beta^* = \sum_{i=1}^{n} \alpha_i^* A_i X_i.$$

- $\beta_0^*$ ???
- Decision function:

$$f(\mathbf{x}) = \langle \beta^*, X \rangle + \beta_0^*.$$

- Classification rule:

$$\text{sgn}\{f(X)\}.$$

# Support Vectors

The KKT conditions imply,

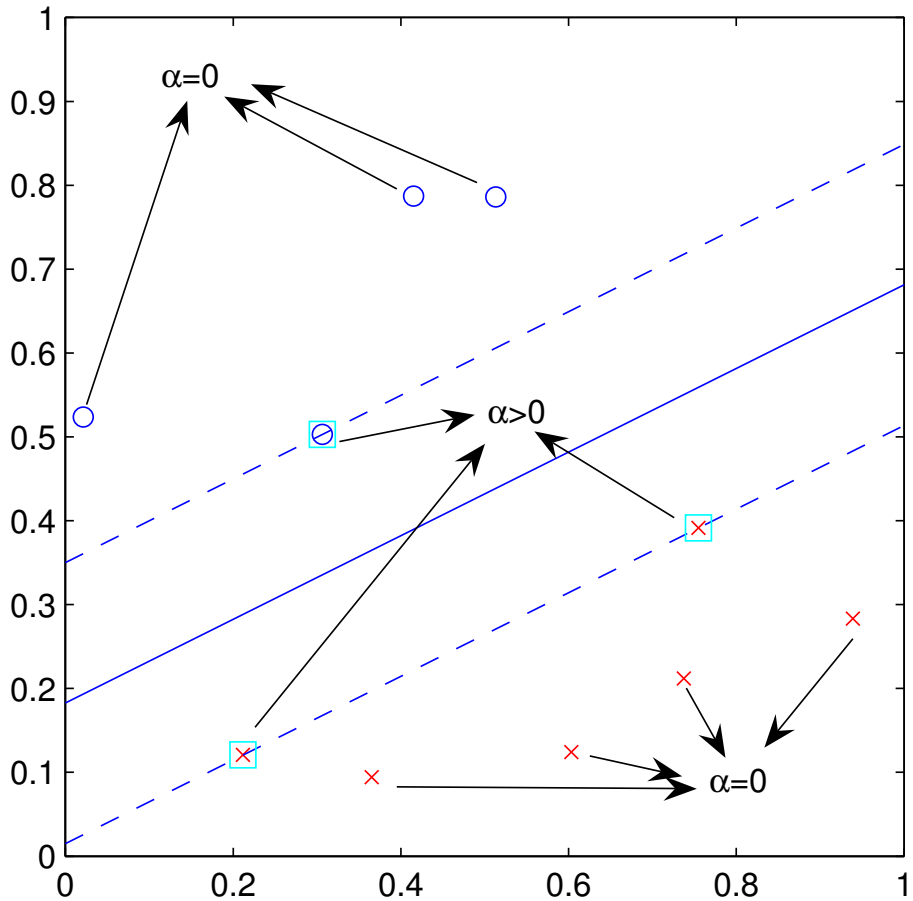
$$\alpha_i^* \left\{ A_i(\beta_0^* + X_i^\top \beta^*) - 1 \right\} = 0.$$

These imply

- If $A_i f^*(X_i) > 1$, then $\alpha_i^* = 0$.
- If $\alpha_i^* > 0$, then $A_i f^*(X_i) = 1$, or in other words, $X_i$ is on the boundary of the "slab".
- The solution $\beta^*$ is defined in terms of a linear combination of the support points.

# Geometric Interpretation: Support Vectors

The $i$-th point is called a support vector if $\alpha_i > 0$




The $i$-th point is a support vector $\implies A_i(\langle \beta^*, X_i \rangle + \beta_0) = 1 \implies \beta_0^* = ...$

# General Case for SVM

- Nonseparable: "zero"-error not attainable $\rightarrow$ "slack variables" $\{\xi_i\}_{i=1}^n$

$$
\begin{aligned}
&\underset{\beta,\beta_0,\xi}{minimize} \frac{1}{2}\|\beta\|^2 + C\sum_{i=1}^{n}\xi_i \\
&\text{subject to} \quad A_i f(X_i) \geq (1-\xi_i), \quad i = 1,\ldots,n, \\
&\qquad\qquad\quad \xi_i \geq 0, \quad i = 1,\ldots,n,
\end{aligned}
$$

where $C > 0$ is a tuning parameter.

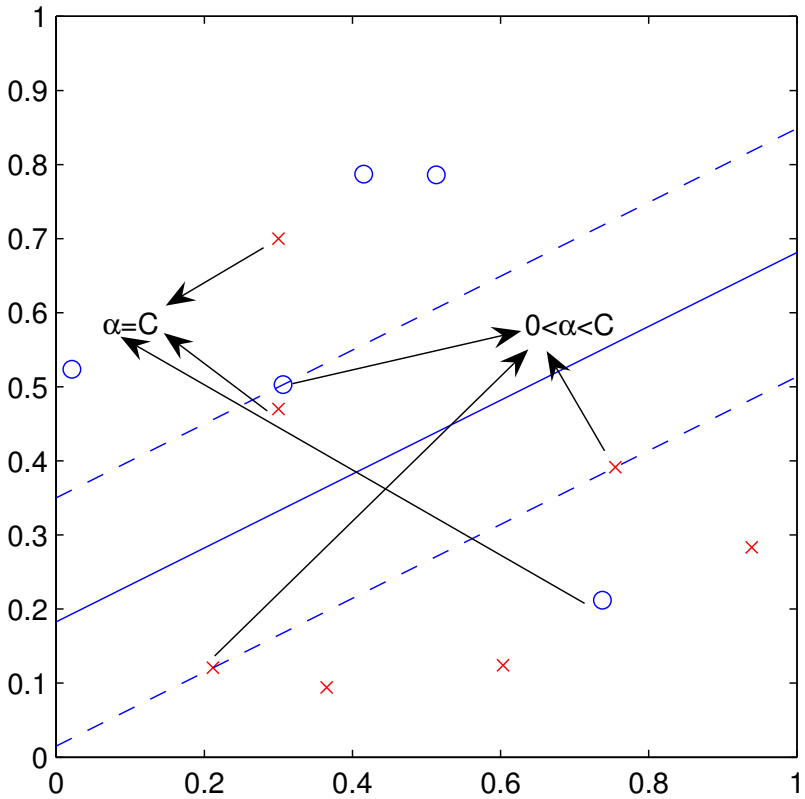
# The Dual Problem for SVM

Substituting into the Lagrange primal, we obtain the Lagrange dual problem as

$$\begin{aligned} \text{minimize} \quad & L_D(\alpha) = \frac{1}{2}\sum_{i,j=1}^{n} \alpha_i \alpha_j A_i A_j \langle X_i, X_j \rangle - \sum_{i=1}^{n} \alpha_i \\ \text{subject to} \quad & 0 \leq \alpha_i \leq C, \quad i = 1, 2, \cdots, n \\ & \sum_{i=1}^{n} \alpha_i A_i = 0. \end{aligned}$$

- Can be solved by quadratic programming.
- Recover $\beta$: $\beta = \sum_{i=1}^{n} \alpha_i A_i X_i$; For given $\beta$, $\beta_0$ can be solved using KKT conditions or Linear Programming (LP).

# Support Vectors




- $\alpha_i = 0 \rightarrow A_i f(X_i) > 1$; not needed in constructing $f(X)$. Support vectors:
- $0 < \alpha_i < C \rightarrow A_i f(X_i) = 1$ (Solve $\beta_0$).
- $\alpha_i = C \rightarrow A_i f(X_i) < 1$.
- Outliers are SVs!

# Reformulation of SVM Optimization

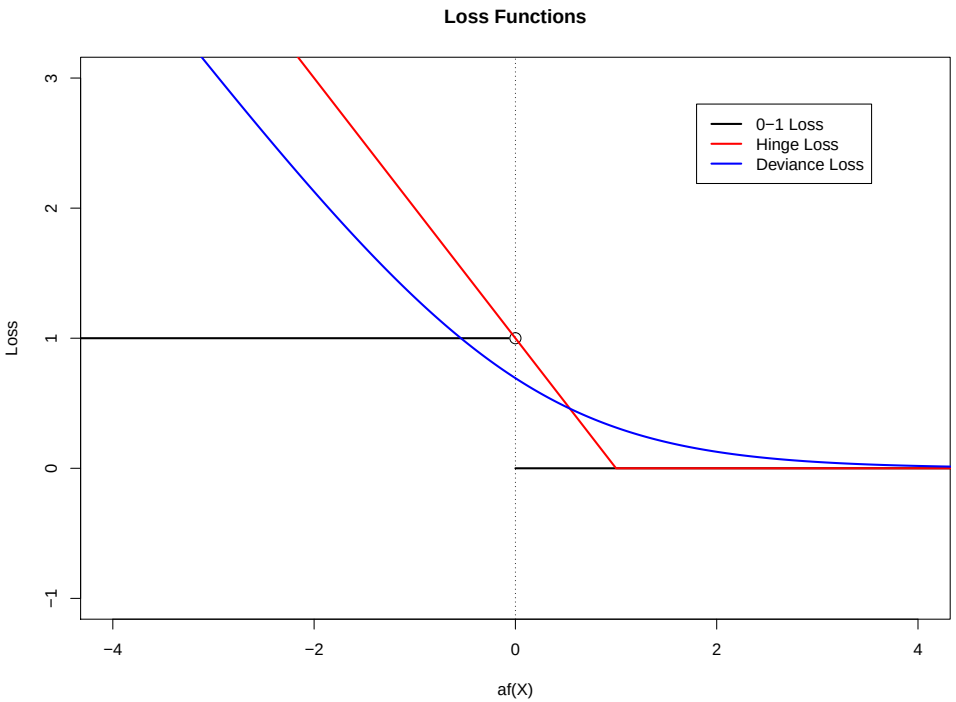
- SVM solves

$$\underset{\beta_0,\beta_1}{minimize} \frac{1}{2}\|\beta\|^2 + C\sum_{i=1}^{n} \ell_{\text{SVM}}\{A_i f(X_i)\}.$$

- $\ell_{\text{SVM}}(u) = (1-u)_+$ (Hinge Loss).
- Nonlinear learning can be achieved by basis expansion or kernel learning.
- Kernel Trick: Replace $\langle X_i, X_j \rangle$ by $K(X_i, X_j)$ and $f(X) = \sum_{i=1}^{n} A_i \alpha_i K(X_i, X) + \beta_0$.

# Loss Functions

To estimate the classifier (threshold),
$\text{sgn}\{\Pr(A = 1|X) - \Pr(A = -1|X)\}$




- 0-1 Loss:
  $\ell\{A, f(X)\} = I\{Af(X) < 0\}.$
- Hinge Loss:
  $\ell\{A, f(X)\} = \{1 - Af(X)\}_+$
- Deviance Loss: $\ell\{A, f(X)\} = \log[1 + \exp\{-Af(X)\}]$

# Classification and Loss Function

Roughly speaking, a good classifier has smaller errors (will add regularization later).

Classification objective function

$$D_o = \underset{D \in R}{\operatorname{argmin}}\, n^{-1} \sum_{i=1}^{n} I\left\{A_i \neq \mathcal{D}(X_i)\right\}.$$

If we compare our ITR objective function as below,

ITR objective function

$$D_o = \underset{D \in R}{\operatorname{argmin}}\, n^{-1} \sum_{i=1}^{n} \frac{Y_i}{p(A_i|X_i)} I\left\{A_i \neq \mathcal{D}(X_i)\right\}.$$

# ITR.SVM

## ITR objective function

$$D_o = \underset{D \in R}{\operatorname{argmin}}\, n^{-1} \sum_{i=1}^{n} \frac{Y_i}{p(A_i|X_i)} I\left\{A_i \neq \mathcal{D}(X_i)\right\}.$$

## ITR.SVM

$$D_o = \underset{D \in R}{\operatorname{argmin}}\, n^{-1} \sum_{i=1}^{n} \frac{Y_i}{p(A_i|X_i)} \ell\{A_i, f(X_i)\} + \frac{\lambda}{2}\|f\|^2_{\mathcal{H}_K}.$$

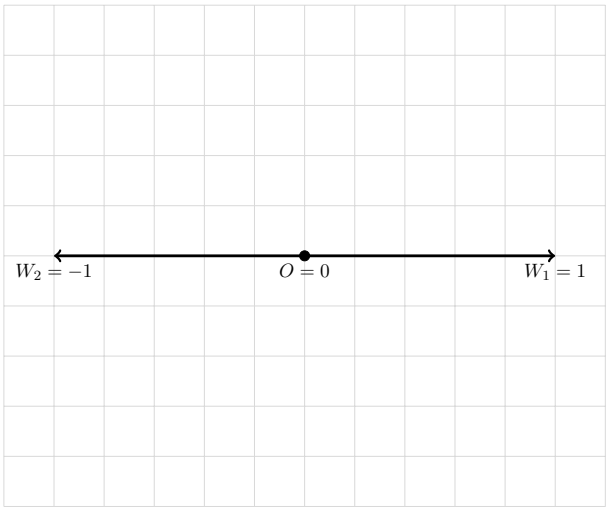
R package: DTRlearn (function: Olearning_Single)

# Outlines

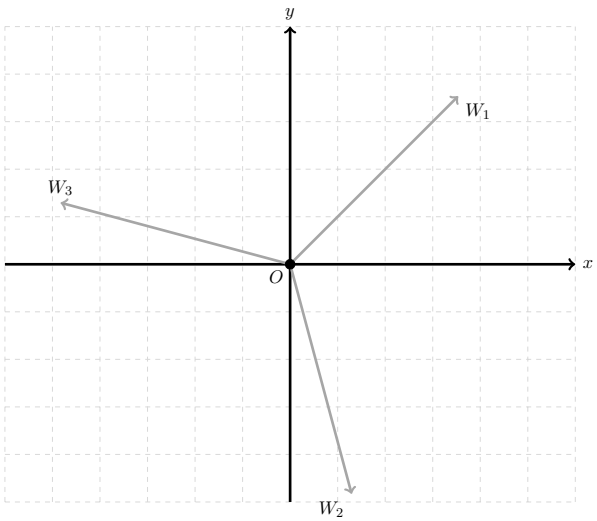
# Multicategory Angle-Based Classification (ABC)

- A simplex based classification structure
- Advantages of ABC (Zhang and Liu, Biometrika, 2014)
  - General structure: binary $\rightarrow$ multicategory
  - Clear geometric interpretation
  - Free of sum-to-zero constraint $\Rightarrow$ faster computational speed
  - Theoretical advantages
  - Numerically competitive

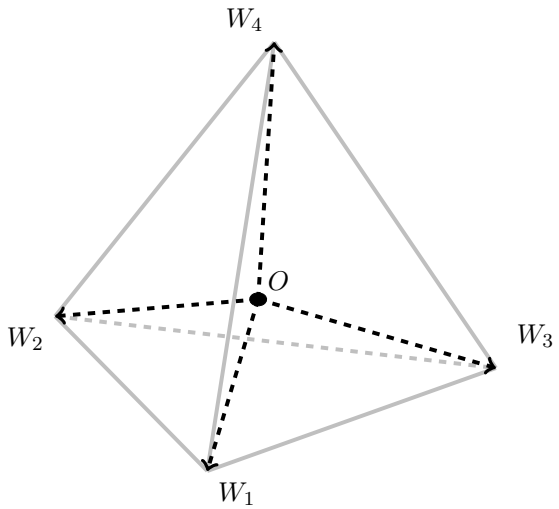
# Illustration of $\{W_i\}$ When $k = 2, 3, 4$.




(a) $k = 2$




(b) $k = 3$



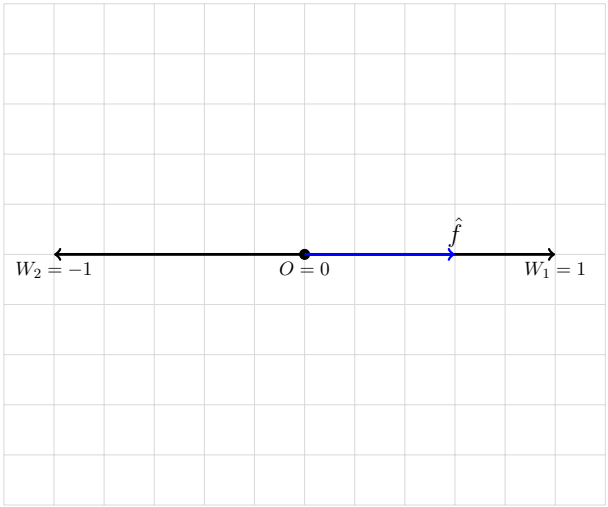

(c) $k = 4$

Remark: When $k = 3$, $\{W_i, i = 1, 2, 3\}$ are the vertices of an equilateral triangle, and when $k = 4$, $\{W_i, i = 1, 2, 3, 4\}$ are the vertices of a regular tetrahedron.

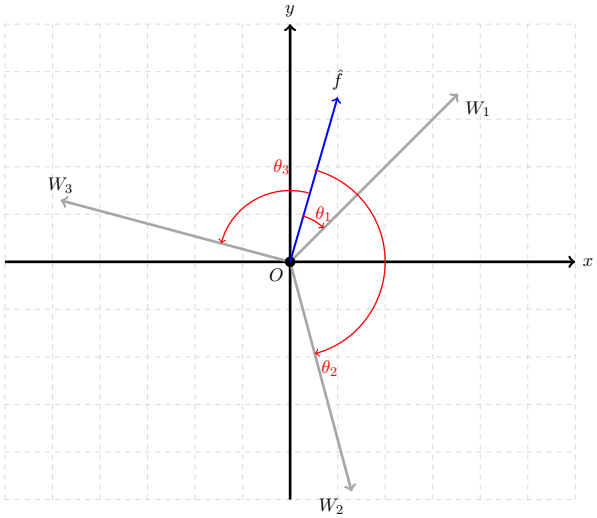
# Angle Based Classifier

- Let $W_j$ represent class $j$.
- Our method is to map $x$ to $\hat{f}(x) \in \mathbb{R}^{k-1}$.
- $\mathcal{A}$ is the class spaces as $\mathcal{A} = \{1, 2, \cdots, k\}$, and $a_i \in \mathcal{A}$ which is the class membership of subject $i$.
- We predict $\hat{a}$ to be the class whose corresponding angle is the smallest, i.e. $\hat{a} = \arg\min_j \angle(W_j, \hat{f})$, where $\angle(\cdot, \cdot)$ denotes the angle between two vectors.
- Minimizing the angle is equivalent to maximize $\langle f(x_i), W_{a_i} \rangle$.

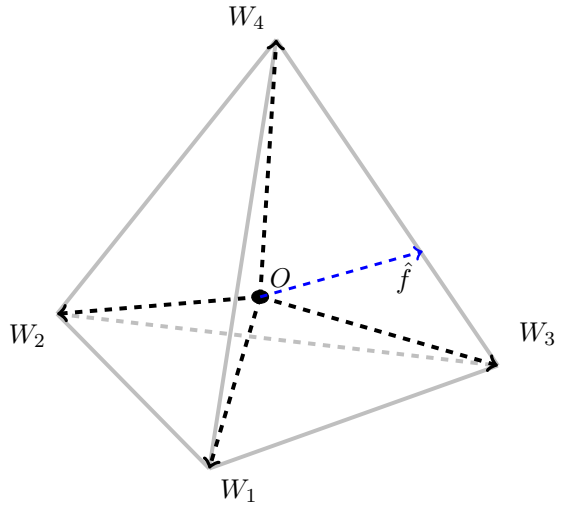
# Angle Based Classifier Illustration




(a) $k = 2$




(b) $k = 3$




(c) $k = 4$

- $k = 2$, $W_1 = 1$ and $W_2 = -1$.
- $k = 3$ (equilateral triangle),
  $W_1 = \left(\frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}}\right), W_2 = \left(\frac{\sqrt{3}-1}{2\sqrt{2}}, -\frac{\sqrt{3}+1}{2\sqrt{2}}\right), W_3 = \left(-\frac{\sqrt{3}+1}{2\sqrt{2}}, \frac{\sqrt{3}-1}{2\sqrt{2}}\right).$
- $k = 4$ (regular tetrahedron),
  $W_1 = \left(\frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}\right), W_2 = \left(\frac{1}{\sqrt{3}}, -\frac{1}{\sqrt{3}}, -\frac{1}{\sqrt{3}}\right), W_3 = \left(-\frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}, -\frac{1}{\sqrt{3}}\right), W_4 = -\left(\frac{1}{\sqrt{3}}, -\frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}\right).$

# Angle Based Classifier

With $\ell$ a convex monotone decreasing function, we have our angle based classifier as,

$$\underset{f \in F}{minimize} \frac{1}{n} \sum_{i=1}^{n} \ell\{\langle f(x_i), W_{a_i} \rangle\} + \lambda J(f). \tag{5}$$

## Example ($k = 2$)

For a binary case, i.e. $k = 2$, $\langle f(x_i), W_{a_i} \rangle = a f(x_i)$,

- When $\ell(\cdot)$ is a deviance loss, $\ell(z) = \log\{1 + \exp(-z)\}$, equation (5) is a logistic regression.
- When $\ell(\cdot)$ is a hinge loss, $\ell(z) = (1 - z)_+$, equation (5) is the support vector machine.

# ITR.ABC

Original objective function,

$$D_o = \underset{D \in R}{\operatorname{argmin}}\, n^{-1} \sum_{i=1}^{n} \frac{Y_i}{p(A_i|X_i)} I\left\{A_i \neq \mathcal{D}(X_i)\right\}.$$

ITR.ABC objective function (Zhang et al., 2017),

$$\underset{f \in F}{minimize} \frac{1}{n} \sum_{i=1}^{n} \frac{Y_i}{\Pr(A_i|X_i)} \ell\{\langle f(x_i), W_{a_i} \rangle\} + \lambda J(f).$$

Ordinal Extension (multiple treatments have a natural order): Chen et al. (2017)